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Title: **The role and regulation of 11 β -hydroxysteroid dehydrogenase type 1 in the inflammatory response.**

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Abbreviations: 11 β -HSD, 11 β -hydroxysteroid dehydrogenase; H6PD, hexose-6-phosphate dehydrogenase; G6PT, glucose-6-phosphate transporter; TNF- α , tumour necrosis factor- α ; M ϕ , macrophage; LPS, lipopolysaccharide; IFN γ , interferon γ ; IL-, interleukin; GM-CSF, granulocyte/macrophage colony-stimulating factor; PMN, polymorphonuclear neutrophils.

Keywords: glucocorticoid, 11 β -hydroxysteroid dehydrogenase, macrophage, mast cell, inflammation, arthritis

SUMMARY

Cortisone, a glucocorticoid hormone, was first used to treat rheumatoid arthritis in humans in the late 1940s, for which Hench, Reichstein and Kendall were awarded a Nobel Prize in 1950 and which led to the discovery of the *anti-inflammatory* effects of glucocorticoids. To be effective, the intrinsically inert cortisone must be converted to the active glucocorticoid, cortisol, by the intracellular action of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1). Whilst orally administered cortisone is rapidly converted to the active hormone, cortisol, by first pass metabolism in the liver, recent work has highlighted an anti-inflammatory role for 11 β -HSD1 within specific tissues, including in leukocytes. Here, we review recent evidence pertaining to the anti-inflammatory role of 11 β -HSD1 and describe how inhibition of 11 β -HSD1, as widely proposed for treatment of metabolic disease, may impact upon inflammation. Finally, the mechanisms that regulate 11 β -HSD1 transcription will be discussed.

PERSPECTIVE; GLUCOCORTICOIDS, 11 β -HSD1 AND INFLAMMATION

Glucocorticoid hormones have diverse physiological effects, co-ordinately regulating pathways in response to external and internal cues. They are part of key homeostatic control mechanisms critical in adapting to environmental challenges and thus are important regulators of intermediary metabolism and the immune system. The anti-inflammatory effects of pharmacological levels of glucocorticoids are well known and widely exploited (reviewed;

(Chapman and Seckl, 2008; McEwen et al., 1997; Smoak and Cidlowski, 2004; Wilckens, 1995; Wilckens and De Rijk, 1997; Yeager et al., 2004)). Endogenous glucocorticoids, however, are immunomodulatory rather than simply anti-inflammatory. Dependent upon concentration and timing, they both enhance and suppress immune reactions, thus shaping both adaptive and innate immune responses (McEwen et al., 1997; Smoak and Cidlowski, 2004; Wilckens, 1995; Wilckens and De Rijk, 1997; Yeager et al., 2004). Endogenous glucocorticoids are essential to survive the lethal effects of pro-inflammatory mediators (IL-1, TNF α , LPS) (Bertini et al., 1988). Conversely, increased gene dosage of glucocorticoid receptor in mice enhances, whereas myeloid cell-specific disruption of the glucocorticoid receptor gene reduces, survival following endotoxic shock (Bhattacharyya et al., 2007; Reichardt et al., 2000). During inflammation, predominantly a response of the innate immune system, glucocorticoids restrain oedema, increase blood viscosity and alter leukocyte distribution/trafficking, haematopoietic differentiation programmes and gene transcription (McEwen et al., 1997). Importantly, they also promote the resolution of inflammation by inducing an anti-inflammatory phenotype in differentiating monocytes (Ehrchen et al., 2007; Giles et al., 2001; Varga et al., 2008), promoting survival of anti-inflammatory macrophages (M ϕ) during inflammation and increasing non-phlogistic phagocytosis of apoptotic neutrophils by M ϕ (reviewed (Heasman et al., 2003; Yona and Gordon, 2007)). Endogenous glucocorticoid activity depends upon glucocorticoid output from the adrenal gland, under the control of the hypothalamic-pituitary-adrenal (HPA) axis and indeed, infection or trauma is a potent stimulus to the HPA axis (Sternberg, 2001). However, *intracellular* glucocorticoid concentrations can differ greatly from blood levels due to the action of 11 β -HSD, an enzyme which interconverts active glucocorticoids (cortisol in humans, corticosterone in rodents) and intrinsically inert 11-keto metabolites (cortisone, 11-dehydrocorticosterone). Two isozymes exist, 11 β -HSD1 and 11 β -HSD2, with predominantly opposite reaction directions *in vivo*, driven by intracellular location and availability of co-substrate (Hewitt et al., 2005; Seckl, 2004). Thus, 11 β -HSD2 inactivates glucocorticoids, whereas 11 β -HSD1 predominantly catalyses the opposite reaction *in vivo*, reactivating glucocorticoids by converting inert 11-keto-glucocorticoids into active forms. Many cells, including immune cells, express 11 β -HSD1, which has the potential to dramatically influence local glucocorticoid availability, within individual cells and within tissues. 11 β -HSD1, including its role in the inflammatory response, has been the subject of a number of recent reviews (eg (Chapman et al., 2006a; Chapman et al., 2006b; Chapman and Seckl, 2008; Draper and Stewart, 2005; Morton and Seckl, 2008; Oppermann, 2006; Seckl, 2004)). Hence, in this review we concentrate on recent data relevant to the role and regulation of 11 β -HSD1 during inflammation.

THE INFLAMMATORY RESPONSE

Inflammation (from the latin, *inflammatio*, to set on fire) is a host defence mechanism activated immediately in response to injury or infection that serves to control and eliminate invading pathogens and promote the repair of damaged tissues. It is characterised by pain, heat, redness and swelling which result from the release of pro-inflammatory mediators (including bioactive amines, lipid mediators and cytokines - typically TNF- α and IL-1) which cause vasodilation and vascular leakage - leading to oedema and permitting leukocyte extravasation - and which generate a chemotactic gradient to guide and activate recruited cells to the site of injury. Resident cells, particularly mast cells and resident M ϕ , are critical in the initiation of an inflammatory response, releasing pro-inflammatory mediators. Polymorphonuclear neutrophils (PMN) and eosinophils are the earliest recruited leukocytes and are crucial to contain microbial infection. As the inflammatory response progresses and the danger from the inciting stimulus lessens and is ultimately removed, there is a progressive

switch in cell types present in the inflamed tissue, with mononuclear cells predominating and resolution ensuing. Persistence of the initiating stimulus invariably leads to chronic inflammation, with the typical dysregulation between destructive inflammatory and excessive healing responses seen in, for eg. rheumatoid arthritis, atherosclerosis and asthma. Thus, it is essential that the early inflammatory response is sufficiently vigorous to protect against infection yet quickly moves into the pro-resolution healing and repair phase once infection is removed, to restore normal homeostasis. Recent evidence suggests that resolution of acute inflammation is an active and highly regulated process (reviewed, (Gilroy, 2004; Savill et al., 2002; Serhan and Savill, 2005)). Moreover, it is likely that mechanisms are engaged, early in the acute inflammatory response, that programme the trajectory and form of the subsequent resolution (Serhan and Savill, 2005). We have proposed that induction of 11 β -HSD1 early during an inflammatory response is one such mechanism (Gilmour et al., 2006).

The key players

The very early events in an acute inflammatory response, through the release of cytokines, chemokines and other mediators, shape the subsequent responses of both the innate and adaptive immune responses, determining the cells that will be recruited and instructing and polarising them. Resident mast cells and M ϕ form a critical part of the first line defence system.

Perhaps best known for their role in allergic disease, mast cells, a highly heterogeneous population of cells, frequently initiate the response to injury and infection. They reside in tissues, usually at epithelial surfaces and around blood vessels and nerves where they act as sentinels to guard against certain bacteria and parasites and where they play a key role in repair processes by promoting angiogenesis and fibrosis (reviewed in (Benoist and Mathis, 2002; Marshall and Jawdat, 2004; Nigrovic and Lee, 2005; Woolley, 2003)). Mast cells are ideally placed at the pinnacle of an inflammatory cell cascade to shape and direct the subsequent immune response. Mast cell mediators cause vasopermeability and oedema (Binstadt et al., 2006) and are important recruiters of leukocytes. Moreover, mast cells are essential in the induction of regulatory T-cell tolerance (Lu et al., 2006). Long implicated in human inflammatory arthritis (Woolley, 2003), recent evidence in mice has highlighted a pivotal role of mast cells in the initiation of inflammatory arthritis initiated by immune complex formation (reviewed, (Nigrovic and Lee, 2005)). Mast cells are important targets for glucocorticoids which inhibit mast cell recruitment, proliferation and survival as well as inhibiting mast cell degranulation, arachidonic acid metabolism and expression and release of cytokines (reviewed, (Kassel and Cato, 2002)), thus partly explaining why glucocorticoids constitute one of the most effective treatments for allergy.

As well as mast cells, M ϕ are also instrumental in dictating the shape of the subsequent immune response. Like mast cells, M ϕ differentiation is also profoundly affected by the microenvironment: cytokines, microbial products and hormones (especially glucocorticoids and vitamin D3) exert potent effects to polarise M ϕ and dictate their phenotype and responses (reviewed, (Gordon and Taylor, 2005; Martinez et al., 2008)). Dendritic cells (DC) represent a specialised cell type of the monocyte-M ϕ lineage and their differentiation and function is also affected by the same factors. Polarised M ϕ exhibit a continuous range of phenotypes. At the extremes, these phenotypes have been categorised as classically activated (or M ϕ 1; type 1) and alternatively activated (or M ϕ 2; type 2) (Martinez et al., 2008). Broadly speaking, the prototypical stimuli IFN γ and LPS polarise M ϕ to the M ϕ 1 phenotype, which are strongly microbicidal and promote strong IL-12-mediated Th1 responses. In contrast, M ϕ 2, which

support Th2 effector responses, exhibit different phenotypes according to the polarising stimuli. These have been categorised as M ϕ 2a (following exposure to IL-4 or IL-13), M ϕ 2b (following exposure to immune complexes in combination with IL-1 β) and M ϕ 2c (a heterogeneous group, following exposure to glucocorticoids, IL-10 or TGF β). The latter group are notable for their “deactivated” phenotype, migrating to sites of infection where they have an enhanced ability to clear debris and apoptotic cells by a non-phlogistic mechanism (Ren et al., 2001) which is, in turn, stimulated by glucocorticoids (Liu et al., 1999), thus actively contributing to the resolution of inflammation (Savill et al., 2002). Intriguingly, it has recently been reported that the anti-inflammatory monocytes induced by glucocorticoids resemble myeloid-derived suppressor cells, a finding with implications for tumour progression under conditions of glucocorticoid excess (Varga et al., 2008).

Although less well characterised than M ϕ , the differentiation of immature DC is similarly influenced by microenvironment, judged by cell surface marker expression, with glucocorticoids having potent effects, for eg modulating appearance of CD1a, a Langerhan’s cell marker, on immature dendritic cells (Freeman et al., 2005). Immature DCs have high endocytic activity and low T-cell activation potential. Once activated within by local microenvironment (eg by encounter with microbes), they migrate to lymph nodes where they present antigen to T- and B-cells to initiate and shape the adaptive immune response.

11 β -HSD1 AND THE INFLAMMATORY RESPONSE

11 β -HSD1 is expressed in immune cells

The cloning of cDNAs encoding 11 β -HSD1 and 11 β -HSD2 since 1989 has allowed the delineation of the expression of the 2 isozymes in specific cells and tissues (reviewed (Seckl and Chapman, 1997)). Although a number of earlier reports demonstrated 11 β -HSD activity in lymphoid organs and/or suggested a role for the enzyme in immunity, they either failed to discriminate between the isozymes or used the non-selective 11 β -HSD inhibitor, glycyrrhetinic acid (Berliner and Dougherty, 1964; Dougherty et al., 1960; Finney and Somers, 1958; Hennebold et al., 1997; Klein et al., 1980; Pompei et al., 1979). The observed anti-viral and anti-inflammatory effects of the latter are more likely attributable to 11 β -HSD2 inhibition (Horigome et al., 1999) than inhibition of 11 β -HSD1.

11 β -HSD1 mRNA and/or protein has recently been reported in several immune cell types, both lymphoid and myeloid, although levels differ greatly between cell types and depend on activation state. In most of these cells, 11 β -HSD1 reductase activity was measured by conversion of cortisone or 11-dehydrocorticosterone to cortisol or corticosterone, respectively, producing some interesting comparisons. Measurements of 11 β -HSD1 activity in intact cells are, however, accompanied by the caveat that the assay necessitates generation of active glucocorticoid which may itself alter cellular differentiation state and/or may regulate 11 β -HSD1 transcription (see below).

Human blood cells contain no detectable 11 β -HSD1 activity (Thieringer et al., 2001). This is in contrast to mice, where 11 β -HSD1 activity was detected in white blood cells, albeit at levels lower than in M ϕ (Gilmour et al., 2006). However, although human monocytes do not express 11 β -HSD1, it is induced upon differentiation to M ϕ (>3pmol cortisol/h/10⁶ cells) (Thieringer et al., 2001). In our own experiments, we have shown expression and activity of 11 β -HSD1 in mouse bone marrow-derived and thioglycollate-elicited peritoneal M ϕ (>5 pmol corticosterone/h/10⁶ cells) (Gilmour et al., 2006). Moreover, although bone marrow-derived M ϕ readily reactivate glucocorticoids (Gilmour et al., 2006), immunofluorescence suggests

that even so, 11 β -HSD1 levels are relatively low in both bone marrow-derived (“resting”) M ϕ and in resident adipose tissue M ϕ from normal lean mice (De Sousa Peixoto et al., 2008). M ϕ expression of 11 β -HSD1 may be highly dependent upon polarisation. Thus, transcriptional profiling of human M ϕ polarisation has shown 9-fold higher 11 β -HSD1 mRNA levels in M ϕ 1 cells (polarised by exposure to LPS and IFN γ) compared to M ϕ 2 cells (polarised by exposure to IL-4) (Martinez et al., 2006). This is consistent with a recent abstract reporting no detectable 11 β -HSD1 activity in human M ϕ polarised to M ϕ 2 by M-CSF, whereas those polarised to M ϕ 1 (with GM-CSF) showed both 11 β -HSD1 activity and 42-fold higher 11 β -HSD1 mRNA levels than M ϕ 2 (Joganathan et al., 2008). It is also consistent with data from the monocyte/M ϕ like cell lines THP-1 and J774.1 in which LPS treatment increased expression of 11 β -HSD1 (Ishii et al., 2007; Thieringer et al., 2001). These findings suggest that 11 β -HSD1 is weakly expressed in resident M ϕ , but is induced following exposure to pro-inflammatory stimuli. A different situation may exist with monocytes that encounter the Th2 polarising cytokines, IL-4 and IL-13 which, in common with 1, 25-dihydroxyvitamin D₃, markedly increased 11 β -HSD1 activity in monocytes (Freeman et al., 2005; Thieringer et al., 2001). Incubation of monocytes with TNF α , IL-1 or LPS had no discernable effect (Thieringer et al., 2001). Differentiation of human monocytes to immature DC (by incubation with GM-CSF and IL-4) was associated with a marked up-regulation of 11 β -HSD1 activity within 2d, peaking at 7d (7pmol cortisol/h/10⁶ cells) which was maintained following maturation by innate immune activating signals (TNF α , Toll-like receptor activation) but which decreased following maturation by CD40 ligation, an adaptive immune activation signal (Freeman et al., 2005). The latter decrease in enzyme activity occurred in the absence of alterations in either 11 β -HSD1 protein levels or mRNA levels, thus must involve a post-translational mechanism (Freeman et al., 2005). Collectively, these findings highlight the exquisite dependence of 11 β -HSD1 expression and regulation upon cellular differentiation state and the local microenvironment. Indeed, 11 β -HSD1 activity in M ϕ is dynamically regulated by pro-resolution mechanisms, being rapidly down-regulated in human monocyte-derived M ϕ following non-phlogistic phagocytosis of apoptotic PMN (Figure 1).

Although 11 β -HSD enzyme activity and the 34kDa 11 β -HSD1 protein are detected in lymphoid organs, levels are low compared to liver and lung (Hennebold et al., 1996). Intriguingly, 11 β -HSD enzyme activity was higher in spleen and peripheral lymph nodes than in mesenteric lymph nodes and Peyer patches, prompting the suggestion that higher 11 β -HSD1 expression is associated with a type 1 cytokine bias, whereas lower 11 β -HSD1 expression is associated with a type 2 response (Hennebold et al., 1996). However, in these studies, the majority of the enzyme activity in lymphoid organs appeared to reside in the stromal cells rather than lymphocytes (Hennebold et al., 1996). This is consistent with the low level of 11 β -HSD1 activity measured in mouse splenic CD4⁺ (0.04 pmol cortisol/h/10⁶ cells), CD8⁺ (0.04 pmol cortisol/h/10⁶ cells), B220⁺ cells (0.015 pmol cortisol/h/10⁶ cells) and thymocytes (0.1 pmol/h/10⁶ cells) (Zhang et al., 2005). Activation of naïve CD4⁺ cells through T cell receptor ligation, or their polarisation into Th1 or Th2 effector cells, resulted in a 2-3-fold increase in 11 β -HSD1 activity (Zhang et al., 2005). However, given that active glucocorticoid is generated during the assay, the possibility of a glucocorticoid effect upon cell differentiation or 11 β -HSD1 expression cannot be excluded. It will be helpful to have measurements of 11 β -HSD1 mRNA levels in these cells without prior glucocorticoid exposure. Interestingly (and consistent with the low activity in M ϕ 2), 11 β -HSD1 mRNA levels measured in splenic Mac-1⁺ cells (a resident population) were only marginally higher than in T cells (Zhang et al., 2005).

Other immune cell types also express 11 β -HSD1. We have recently shown high expression of 11 β -HSD1 in mast cells (Coutinho et al, manuscript in preparation), a finding with implications for inflammation, infection, allergy and tolerance (see above). Expression of 11 β -HSD1 and its cofactor generating partner H6PDH in human PMN has recently been reported (Kardon et al., 2008). This study also highlighted the potential for 11 β -HSD1 to influence apoptosis in PMN. PMN take up vast amounts of glucose during an inflammatory reaction (Jones et al., 1994), at least some of which will be transported into the endoplasmic reticulum via the glucose-6-phosphate transporter (G6PT). Congenital deficiency in G6PT or inhibition of its function in PMN causes granulocyte apoptosis (Leuzzi et al., 2003), which has been linked to depletion of NADPH in the endoplasmic reticulum (Kardon et al., 2008). However, only high pharmacological levels of cortisol (and not cortisone) were effective in preventing apoptosis (Kardon et al., 2008) and the physiological relevance of these findings remain to be established. Aged (>60% apoptotic) human PMN do not show 11 β -HSD1 reductase activity (Figure 1).

To date, 11 β -HSD2 has not been reported in rodent leukocytes. Circulating mouse white blood cells do not express 11 β -HSD2 mRNA (Gilmour et al., 2006) and 11 β -HSD2 mRNA is absent from mouse M ϕ (Gilmour et al., 2006), DC (Zhang et al., 2005), lymphocytes (Zhang et al., 2005) and mast cells (Coutinho et al, manuscript in preparation). Similarly, 11 β -HSD2 mRNA is not detected in human blood from normal individuals (Thieringer et al., 2001) and it is absent or at negligible levels in normal human monocytes (Freeman et al., 2005; Thieringer et al., 2001), M ϕ (Thieringer et al., 2001) and DC (Freeman et al., 2005). However, 11 β -HSD2 has been reported in human leukocytes in pathological conditions. Microarray studies have shown *transient* expression of 11 β -HSD2 in peripheral blood mononuclear cells in patients with early rheumatoid arthritis (Olsen et al., 2004) and 11 β -HSD2 expression is elevated in transformed B cell lines established from rheumatoid arthritis patients compared to their twin (non-arthritic) controls (Haas et al., 2006). Immunohistochemical (IHC) staining has demonstrated 11 β -HSD1 and 11 β -HSD2 in synovial M ϕ in both osteoarthritis and rheumatoid arthritis patients (Schmidt et al., 2005) and this has since been corroborated with a distinct antibody (Haas et al., 2006; Hardy et al., 2008) and, more recently, with inhibitor studies (Hardy et al., 2008). The significance of these findings remain to be established, but it is noteworthy that 11 β -HSD2 is widely expressed in embryonal development and is found in many transformed cells lines, but is highly restricted in mature tissues and primary cells. Whilst it is not expressed in normal leukocytes, it is expressed in a number of epithelial cell types, where current evidence suggests it is *down-regulated* by pro-inflammatory mediators (see below). The expression of 11 β -HSD2 in M ϕ in chronically inflamed synovium of rheumatoid arthritis may be an adaptation to allow increased cell proliferation and/or might reflect an altered differentiation programme in the inflammatory microenvironment. Nevertheless, these findings highlight that intracellular glucocorticoid action may be very different in the chronic inflammatory condition to that prevailing in an acute inflammatory response.

11 β -HSD1 and 2 are regulated during an inflammatory response

As might be predicted from the anti-inflammatory effects of glucocorticoids, in general, 11 β -HSD1 expression is increased and 11 β -HSD2 decreased by pro-inflammatory stimuli or during inflammation. *In vivo*, 11 β -HSD1 expression was rapidly and markedly increased in immune cells elicited in the peritoneum of mice during sterile peritonitis (Gilmour et al., 2006). In human and rodent colitis, colonic 11 β -HSD1 was strongly up-regulated and 11 β -HSD2 down-regulated (Bryndova et al., 2004; Vagnerova et al., 2006; Zbankova et al., 2007).

In rheumatoid (but not osteo-) arthritis, within the joint, synovial inflammation (increased cellularity) was positively associated with cortisone reactivation, suggesting increased synovial 11 β -HSD1 activity despite the expression of 11 β -HSD2 in synovial M ϕ (Schmidt et al., 2005). This is consistent with more recent reports of increased 11 β -HSD1 activity and mRNA levels in synovial tissues of patients with rheumatoid arthritis (Hardy et al., 2008). However, although 11 β -HSD1 was expressed in leukocytes in the rheumatic synovium, the main site of expression was in synovial fibroblasts where it was highly induced by IL-1 or TNF α (Hardy et al., 2006; Hardy et al., 2008). The functional relevance was illustrated by the efficacy of *cortisone* in suppressing production of IL-6 by synovial fibroblasts, an effect abolished by the non-selective 11 β -HSD inhibitor, glycyrrhetinic acid (Hardy et al., 2006). In obesity, where adipose tissue inflammation is now considered a cardinal feature, 11 β -HSD1 activity and mRNA is increased in adipose tissue, whereas expression in liver is normal or reduced (reviewed, (Seckl et al., 2004)). During ovulation, an inflammatory-like response with “injury” (ovulation) and “resolution” (luteinising) phases, 11 β -HSD1 and 11 β -HSD2 exhibit a switch in expression in granulosa cells. Prior to ovulation 11 β -HSD2 but not 11 β -HSD1 is expressed, rendering granulosa cells glucocorticoid insensitive. Following ovulation, only 11 β -HSD1 is switched on in luteinised granulosa cells, being further increased by IL-1 β (Tetsuka et al., 1999; Tetsuka et al., 1997). In addition, prostaglandins may increase 11 β -HSD1 activity in luteinised granulosa cells (Jonas et al., 2006) (as well as in chorion trophoblast cells (Alfaidy et al., 2001)), although the prostaglandin induction of activity appeared to be mediated post-translationally. Ovarian surface epithelial cells also express 11 β -HSD1 where again, expression is increased by IL-1 (Yong et al., 2002). Induction of 11 β -HSD1 expression and activity by pro-inflammatory mediators in the ovary may minimise inflammatory tissue damage following ovulatory rupture. A similar reciprocal regulation of 11 β -HSD1 and 2 occurs in other non-immune cell types including human MG-63 osteosarcoma cells (Cooper et al., 2001) and human aortic smooth muscle cells (Cai et al., 2001). In both cases, IL-1 β or TNF- α simultaneously increased 11 β -HSD1 expression and down-regulated 11 β -HSD2 (Cai et al., 2001; Cooper et al., 2001). However, although IL-1 β increased 11 β -HSD1 expression in primary mouse aortic smooth muscle cells, it was without effect on mouse aortic rings and systemic inflammation following LPS injection in mice had only a modest effect upon vascular 11 β -HSD1 activity (Dover et al., 2007). Furthermore, although TNF α and IL-1 β increased 11 β -HSD1 mRNA levels in primary human pre-adipocytes (Tomlinson et al., 2001) as well as 3T3-L1 preadipocytes (Arai et al., 2007), they had no effect in 3T3-L1 adipocytes (Arai et al., 2007). Nevertheless, a consistent picture emerges where proinflammatory mediators, particularly TNF- α and IL-1 β , increase 11 β -HSD1 expression whilst concomitantly decreasing 11 β -HSD2, albeit in a cell-specific manner, promoting local glucocorticoid availability and hence local anti-inflammatory action. Although the magnitude of the effects differ greatly between cell types, pro-inflammatory mediators also increase 11 β -HSD1 activity in rat mesangial cells (Escher et al., 1997) and synergise with glucocorticoid to increase expression in cultured human amnion fibroblasts (Sun and Myatt, 2003). Dysregulation of the normal reciprocal regulation of 11 β -HSD1 and 11 β -HSD2 may contribute to the failure of resolution during chronic inflammation. As noted above, normal M ϕ do not express 11 β -HSD2, although it is expressed in rheumatoid arthritis synovial M ϕ (Hardy et al., 2008). Moreover, whereas normal human M ϕ increased 11 β -HSD1 mRNA levels by 4.5-fold within 3h of IL-10 addition, in rheumatoid arthritis synovial M ϕ , IL-10 failed to increase expression of 11 β -HSD1 (and a subset of other IL-10 inducible genes) (Antoniv and Ivashkiv, 2006). This suggests a maladaptive mechanism in chronic inflammation resulting in imbalanced 11 β -HSD activities that is likely to result in reduced intracellular glucocorticoid action in synovial M ϕ and even local glucocorticoid resistance, at

least with glucocorticoids that are substrates for 11 β -HSD (eg prednisolone). Few reports exist of 11 β -HSD1 expression during infection. 11 β -HSD1 mRNA levels were unaltered in skin lesions of leprosy patients compared to skin of borderline leprosy patients without lesions (Andersson et al., 2007). However, Rook and colleagues have shown that cortisone reactivation is increased in tuberculosis and inferred increased activity of 11 β -HSD1 in lung (Baker et al., 2000). Moreover, they have proposed that an immune response associated with a Th1 cytokine profile increases glucocorticoid reactivation by 11 β -HSD1, promoting a transition towards a Th2 response. They further suggest that eventually, in the presence of Th2 cytokine polarisation, there is a further shift to cortisol inactivation (Rook et al., 2000). Certainly the current data from rheumatoid arthritis would be consistent with this notion, but clearly this can only be a partial explanation of the local glucocorticoid resistance that frequently arises during chronic inflammation.

11 β -HSD1 amplifies glucocorticoid action in vivo

The predominant oxo-reductase reaction catalysed by 11 β -HSD1 in intact cells logically points to a role in glucocorticoid amplification. In older studies using non-selective inhibitors of 11 β -HSD, interpretation was always confounded by the predominant inhibition of renal glucocorticoid inactivation by 11 β -HSD2. However, over the last decade our understanding of the *in vivo* role of 11 β -HSD1 has been hugely progressed by the generation of mice homozygous for a targeted disruption of the *Hsd11b1* gene, encoding 11 β -HSD1 (Kotelevtsev et al., 1997). The phenotype of these mice, as well as that of transgenic mice with tissue-specific alterations in 11 β -HSD1 has been recently reviewed (Paterson et al., 2005). Whilst basal plasma corticosterone levels are increased in *Hsd11b1*^{-/-} mice on a mixed MF1/129 genetic background (Kotelevtsev et al., 1997), on the C57BL/6J background, these mice have normal blood glucocorticoid levels (Yau et al., 2007) and yet a phenotype consistent with intracellular glucocorticoid deficiency. They show increased insulin sensitivity and are protected against metabolic disease (Morton et al., 2001; Morton et al., 2004), show increased angiogenesis following injury (Small et al., 2005) and resist cognitive decline in old age (Yau et al., 2007; Yau et al., 2001). More recently, mice have also been generated which are deficient in hexose-6-phosphate dehydrogenase, the “partner” enzyme to 11 β -HSD1 that dictates its enzyme direction through cofactor supply within the endoplasmic reticulum lumen (Lavery et al., 2006). In *H6pd*^{-/-} mice, the normal reaction direction of 11 β -HSD1 is reversed so that it functions exclusively as a dehydrogenase, inactivating glucocorticoids (Lavery et al., 2006). Their phenotype is similar to that of *Hsd11b1*^{-/-} mice in that they also show increased insulin sensitivity and alterations in glucose and lipid homeostasis (Bujalska et al., 2008). Indeed, mutations in the *H6PD* gene are responsible for cortisone reductase deficiency in humans (Lavery et al., 2008a), a syndrome originally thought to be due to mutation in the *HSD11B1* gene. However, *H6pd*^{-/-} mice show other abnormalities not observed in *Hsd11b1*^{-/-} mice, most notably skeletal myopathy, possibly as a consequence of altered redox state in the endoplasmic reticulum (Lavery et al., 2008b).

Hsd11b1^{-/-} mice have an exaggerated inflammatory response and altered resolution mechanisms

In vivo, during sterile peritonitis, M ϕ from *Hsd11b1*^{-/-} mice showed delayed acquisition of phagocytic competence compared to wild type controls, with more free apoptotic PMN two days following injection with thioglycollate (Gilmour et al., 2006). *In vitro*, 11-dehydrocorticosterone (the 11 β -HSD1 substrate in rodents) was equipotent with corticosterone in promoting M ϕ phagocytosis of apoptotic PMN, but was without effect on M ϕ from *Hsd11b1*^{-/-} mice (Gilmour et al., 2006). Glucocorticoid receptors in M ϕ have been

implicated as the target for the protective effects of glucocorticoids against endotoxaemia (Bhattacharyya et al., 2007). Recent evidence suggests 11 β -HSD1 in M ϕ makes an important contribution to endogenous glucocorticoid action in the systemic response to endotoxin. Following LPS administration, *Hsd11b1*^{-/-} mice exhibited greater weight loss and higher serum levels of TNF- α , IL-6 and IL-12p40 compared to their wild-type counterparts (Zhang and Daynes, 2007). Furthermore, although no differences were detected *in vitro* between bone marrow-derived M ϕ from *Hsd11b1*^{-/-} and control mice, *ex vivo*, thioglycollate-elicited peritoneal M ϕ from *Hsd11b1*^{-/-} mice showed a greater cytokine response to LPS (Gilmour et al., 2006; Zhang and Daynes, 2007), illustrating that exposure to 11 β -HSD1 substrate (*in vivo*) must affect the differentiation or activation state of M ϕ .

More recently, in a mouse model of self-resolving experimental arthritis, we have found that the onset of inflammation (redness and swelling) occurs earlier in *Hsd11b1*^{-/-} mice compared to control mice (Coutinho et al, manuscript in preparation) and resolution is delayed (unpublished data), suggesting a role for 11 β -HSD1 both in restraining acute inflammation and promoting its resolution. Mast cells are critical in the initiation of inflammation in this model (Lee et al., 2002). Given our recent finding of 11 β -HSD1 expression in mast cells (Coutinho et al, manuscript in preparation) it will be important to elucidate the contribution of mast cell 11 β -HSD1 to the acute inflammatory phenotype of *Hsd11b1*^{-/-} mice. Moreover, studies on the effects of selective 11 β -HSD1 inhibitors on the inflammatory response are now warranted, to distinguish effects due to altered hormonal environment/differentiation of immune cells in *Hsd11b1*^{-/-} mice from those acutely due to reduced or absent 11 β -HSD1 activity.

11 β -HSD1 as a therapeutic target

Whilst the short-term benefits of elevated glucocorticoid levels are self-evident, in the long term, elevated blood levels of glucocorticoids whether extreme, as in Cushing's Disease or pharmacological, following prescription usage of glucocorticoids, have deleterious side-effects, including hypertension, insulin resistance and increased cardiovascular disease risk (Souverein et al., 2004; Wei et al., 2004). Because of the striking phenotypic similarities between Cushing's Syndrome and Metabolic Syndrome, it was proposed that in the absence of excessive blood glucocorticoid levels, elevated *intracellular* levels of glucocorticoids through increased activity of 11 β -HSD1, especially in adipose tissue, might be causative in Metabolic Syndrome (Seckl et al., 2004). Indeed, this idea has gained considerable support from the phenotype of *Hsd11b1*^{-/-} mice, protected from metabolic disease, and from transgenic mice with ectopic overexpression of 11 β -HSD1 in lipid storing cells (under the control of the aP2 promoter) which exhibit all the major components of the Metabolic Syndrome (reviewed (Seckl et al., 2004)). These data highlighted 11 β -HSD1 as a promising drug target for treatment of insulin resistance, diabetes and even cardiovascular disease. Indeed, to date, over 100 patents exist on 11 β -HSD1 inhibitors and initial data, at least for the treatment of diabetes (Alberts et al., 2003; Wang et al., 2006) and atheroma (Hermanowski-Vosatka et al., 2005), and even, possibly, improvement of cognitive function (Sandeep et al., 2004) appear promising. Thus, paradoxically, deficiency in 11 β -HSD1 is associated with worsened acute inflammation yet inhibition improves outcome in chronic inflammatory conditions often associated with over-nutrition. An important caveat to the studies described above on the inflammatory phenotype of *Hsd11b1*^{-/-} mice is that they were all conducted in young, lean, healthy mice and may not extrapolate to pathogenic situations. Over-nutrition (obesity, type 2 diabetes, metabolic syndrome) is associated with a dysregulated immune response (Hotamisligil, 2006), and impaired resistance to bacterial infection, exemplified by

the recent emergence of an association between mortality due to sepsis and obesity (Vachharajani, 2008), also observed in mice (eg (Amar et al., 2007)). It will be important to dissect the complex relationships between over-nutrition, glucocorticoid status and the immune system. At this stage, with 11 β -HSD1 inhibitors in clinical trials, it is vital to firmly establish and define the role of 11 β -HSD1 in limiting and resolving inflammation lest metabolically beneficial drugs are complicated by pro-inflammatory side-effects.

THE TRANSCRIPTIONAL REGULATION OF 11 β -HSD1

A clear understanding of the transcriptional regulation of the gene encoding 11 β -HSD1 is crucial to understanding the molecular basis for its dysregulation during obesity and to most effectively target inhibition. The transcriptional regulation of the *HSD11B1* gene is highly tissue-specific, illustrated by the selective increase in adipose 11 β -HSD1 mRNA levels in obesity, and the tissue-specific effects of pro-inflammatory mediators (reviewed above). Glucocorticoids themselves up-regulate 11 β -HSD1 mRNA levels in a variety of primary cells *in vitro* (Bujalska et al., 1999; Cooper et al., 2002; Engeli et al., 2004; Hammami and Siiteri, 1991; Jamieson et al., 1995; Sun et al., 2002; Whorwood et al., 2001) although regulation *in vivo* is tissue-specific and considerably more complex (Hundertmark et al., 1994; Jamieson et al., 1999; Jellinck et al., 1997; Michailidou et al., 2007; Yang et al., 1994). However, to date, all the evidence points to a crucial role for the C/EBP family of transcription factors in both the basal and the regulated transcription of 11 β -HSD1.

The *Hsd11b1* gene is transcribed from 3 promoters; P1, P2 and P3 (Bruley et al., 2006; Moisan et al., 1992). Transcription in liver, brain and adipose tissue is predominantly from P2 and is dependent upon C/EBP α (Bruley et al., 2006; Williams et al., 2000). Transcription from P1 is C/EBP α -independent; P1 is the main promoter used in lung (Bruley et al., 2006). P3, described in rat kidney, is located within the intron between exons 2 and 3 (Moisan et al., 1992). It encodes a truncated protein missing the N-terminus of 11 β -HSD1 and although the truncated protein can be detected *in vivo*, *in vitro* it shows no enzyme activity (Mercer et al., 1993). P3 is also used in mouse kidney, but is transcribed at negligible levels in other mouse tissues (unpublished data). The regulation of the P1 and P3 promoters remains uncharacterised.

In vivo, C/EBP α is the major regulator of *Hsd11b1* in liver and brown adipose tissue (Bruley et al., 2006). It is likely to play a similar central role in white adipose tissue, although this has not been directly tested. Whilst several other transcription factors have been shown to regulate 11 β -HSD1 in liver or adipose, most are likely to act indirectly on the P2 promoter. Thus, PPAR α (Hermanowski-Vosatka et al., 2000), PPAR γ (Berger et al., 2001), HNF1 α (Shih et al., 2001) and LXR α (Stulnig et al., 2002) all decrease 11 β -HSD1 mRNA levels, but none act directly. Similarly, glucocorticoid regulation of *HSD11B1* gene transcription, at least in human skin fibroblasts and A549 lung epithelial cells is indirect (Hammami and Siiteri, 1991; Sai et al., 2008). In the latter, glucocorticoid induction requires C/EBP β binding to the P2 promoter (Sai et al., 2008). In human amnion fibroblasts, C/EBP α has been implicated in the glucocorticoid regulation, acting together with glucocorticoid receptor to bind to and regulate the P2 promoter (Yang et al., 2007). In 3T3-L1 cells, induced to differentiate into adipocytes, it is again C/EBP β that mediates the effect of cAMP to increase promoter activity (Gout et al., 2006). Similarly, treatment of 3T3-L1 preadipocytes with ceramide or the AMPK activator, AICAR, increased 11 β -HSD1 mRNA levels, dependent upon C/EBP β binding to the P2 promoter (Arai et al., 2007). It is curious therefore, that C/EBP β , an activator of the P2 promoter in preadipocytes and A549 cells, is only a weak activator in hepatoma cells, acting

as a relative repressor *in vivo* in liver and in hepatoma cells co-transfected with C/EBP α (Williams et al., 2000). We believe it likely that C/EBP α action predominates in liver, where it is expressed at high levels (Landschulz et al., 1988). In cells with more modest levels of C/EBP α or none at all, C/EBP β , if it receives the appropriate post-translational signals or is increased to sufficiently high levels, activates the 11 β -HSD1 P2 promoter. A549 cells contain very low levels of C/EBP α , as do 3T3-L1 preadipocytes (Cao et al., 1991; Li et al., 1995; Sai et al., 2008). C/EBP α , essential for myeloid cell differentiation (Zhang et al., 1997) and a neonatal inflammatory response (Burgess-Beusse and Darlington, 1998) has been shown to decrease the transactivation potential of C/EBP β through control of isoforms expressed (Burgess-Beusse et al., 1999) and thus may suppress transactivation by C/EBP β in liver under normal circumstances. Further elucidation of the role in transcriptional control of 11 β -HSD1 played by the C/EBP family of transcription factors will be highly informative. Other members of the C/EBP family than C/EBP α are also major regulators of immune cell fate and differentiation pathways (Lekstrom-Himes, 2001; Nerlov, 2007).

CONCLUSIONS AND FUTURE PROSPECTS

Whilst remarkable progress has been made over the last decade to elucidate the physiological role(s) of 11 β -HSD1, much remains unknown. Given the importance of 11 β -HSD1 as a drug target for insulin resistance, diabetes and possibly cardiovascular disease, it is crucial to understand the consequences of its inhibition or deficiency for both acute and chronic inflammatory disease. It is now vital to determine whether and how cellular differentiation pathways, particularly of M ϕ and mast cells, are altered in 11 β -HSD1-deficiency/inhibition and to understand the mechanisms that underlie tissue-specific regulation and dysregulation of the *HSD11B1* gene.

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FIGURE LEGENDS

Figure 1: 11β -HSD1 activity is down-regulated in human monocyte-derived M ϕ after phagocytosis of aPMNs

Human monocyte-derived M ϕ were obtained and cultured as previously described (Liu et al., 1999). 11β -HSD1 activity in cultures of human monocyte-derived M ϕ s was measured by conversion of 200nM A to B over 24h as previously described (Gilmour et al., 2006). Both cell number (data not shown) and 11β -HSD1 activity remain constant over this culture period but 11β -HSD1 activity was reduced by 25% after an *in vitro* phagocytosis assay performed as

previously described (Gilmour et al., 2006) at d4 in which 20% of Mφs ingested aged PMNs (>60% apoptotic; data not shown). Aged PMNs did not contribute to the $^{11}\beta$ -activity measured. Values are Mean +/- SD of 3 separate experiments carried out in duplicate. *P<0.05.

Figure 1